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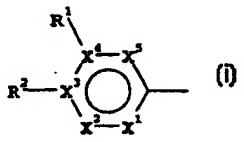
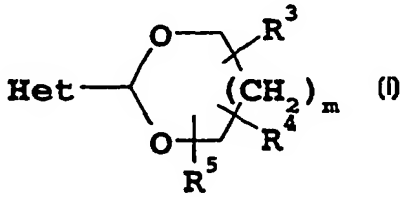
(54) Title: HETEROARYL-CYCLIC ACETALS



(I)



(I)

(57) Abstract

Compounds of formula (I) are described in which Het is a five or six membered heteroaromatic ring of formula (i) in which one of $R^1$ and $R^2$ is optionally substituted heteroaryl and the other is optionally substituted heteroaryl or optionally substituted aryl; $X^1$ is a bond, $X^3$ and $X^4$ are each independently N or C and $X^2$ and $X^5$ are independently CH, N, NH, O or S; or $X^3$ and $X^4$ are C, one of $X^1$, $X^2$ and $X^5$ is N and the others are N or CH; but excluding compounds in which $X^1$ is a bond, one of $X^2$ and $X^5$ is N and the other is NH and $X^3$ and $X^4$ are both C; $R^3$ represents a group $-L^1-R^6$; $R^4$ represents hydrogen, alkyl or hydroxyalkyl; or $R^3$ and $R^4$, when attached to the same carbon atom, may form with the said carbon atom a cycloalkyl, cycloalkenyl or heterocycloalkyl ring or a group $C=CH_2$; $R^5$ represents hydrogen or alkyl; and m is zero or an integer 1 or 2; and N-oxides thereof, and their prodrugs; and pharmaceutically acceptable salts and solvates of compounds of formula (I) and N-oxides thereof, and their prodrugs. The compounds are TNF inhibitors and are useful as pharmaceuticals.

# HETEROARYL-CYCLIC ACETALS

This invention is directed to heteroaryl-cyclic acetals, their preparation, pharmaceutical compositions containing these compounds, and their pharmaceutical use in the treatment of disease states capable of being modulated by the inhibition of TNF.

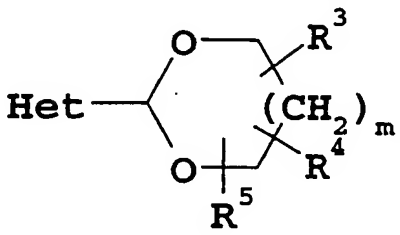
Tumour necrosis factor (TNF) is an important pro-inflammatory cytokine which causes hemorrhagic necrosis of tumors and possesses other important biological activities. TNF is released by activated macrophages, activated T-lymphocytes, natural killer cells, mast cells and basophils, fibroblasts, endothelial cells and brain astrocytes among other cells.

The principal in vivo actions of TNF can be broadly classified as inflammatory and catabolic. It has been implicated as a mediator of endotoxic shock, inflammation of joints and of the airways, immune deficiency states, allograft rejection, and in the cachexia associated with malignant disease and some parasitic infections. In view of the association of high serum levels of TNF with poor prognosis in sepsis, graft versus host disease and adult respiratory distress syndrome, and its role in many other immunologic processes, this factor is regarded as an important mediator of general inflammation.

TNF primes or activates neutrophils, eosinophils, and endothelial cells to release tissue damaging mediators and increase the expression of adhesion molecules. In fibroblasts, TNF stimulates the production of collagenase, an enzyme implicated in the joint destruction in rheumatoid arthritis. TNF also activates monocytes, macrophages and T-lymphocytes to cause the production of colony stimulating factors and other pro-inflammatory cytokines such IL-1, IL-6, IL-8 and GM-CSF, which in some cases mediate the end effects of TNF. The ability of TNF to activate T-lymphocytes, monocytes, macrophages and related cells has been implicated in the progression of Human Immunodeficiency Virus (HIV) infection. In order for these cells to become infected with HIV and for HIV replication to take place the cells must be maintained in an activated state. Cytokines such as TNF have been shown to activate HIV replication in monocytes and macrophages. Features of endotoxic shock such as fever, metabolic acidosis, hypotension and intravascular coagulation are thought to be mediated through the actions of TNF. The cachexia associated with certain disease states is mediated through indirect effects on protein catabolism. TNF also promotes bone resorption and acute phase protein synthesis.

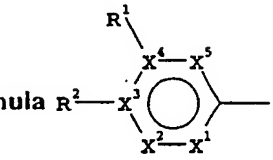
TNF-alpha inhibits surfactant protein C gene transcription, which may contribute to abnormalities of surfactant homeostasis associated with pulmonary injury and infection, induces

Thus, in one aspect, the present invention is directed to compounds of general formula (I)



(I)

wherein:-

Het is a five or six membered heteroaromatic ring of the formula  in which

one of $R^1$ and $R^2$ is optionally substituted heteroaryl and the other is optionally substituted heteroaryl or optionally substituted aryl; $X^1$ is a bond, $X^3$ and $X^4$ are each independently N or C and $X^2$ and $X^5$ are independently CH, N, NH, O or S; or $X^3$ and $X^4$ are C, one of $X^1$, $X^2$ and $X^5$ is N and the others are N or CH; but excluding compounds in which $X^1$ is a bond, one of $X^2$ and $X^5$ is N and the other is NH and $X^3$ and $X^4$ are both C;

$R^3$ represents a group $-L^1-R^6$;

$R^4$ represents hydrogen, alkyl or hydroxyalkyl; or

$R^3$ and $R^4$, when attached to the same carbon atom, may form with the said carbon atom a cycloalkyl, cycloalkenyl or heterocycloalkyl ring or a group $C=CH_2$;

$R^5$ represents hydrogen or alkyl;

$R^6$ is hydrogen, alkyl, azido, hydroxy, alkoxy, aryl, arylalkyloxy, aryloxy, carboxy (or an acid bioisostere), cycloalkyl, cycloalkyloxy, heteroaryl, heteroarylalkyloxy, heteroaryloxy, heterocycloalkyl, heterocycloalkyloxy, nitro, $-NY^1Y^2$, $-N(R^7)-C(=Z)-R^8$, $-N(R^7)-C(=Z)-L^2-R^9$, $-NH-C(=Z)-NH-R^8$, $-NH-C(=Z)-NH-L^2-R^9$, $-N(R^7)-SO_2-R^8$, $-N(R^7)-SO_2-L^2-R^9$, $-S(O)_nR^{10}$, $-C(=Z)-NY^1Y^2$ or $-C(=Z)-OR^{10}$;

$R^7$ is hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl, or heterocycloalkyl;

$R^8$ is alkyl, alkoxy, aryl, arylalkyloxy, cycloalkyl, heteroaryl, heteroarylalkyloxy or heterocycloalkyl;

$R^9$ is alkoxy, aryl, arylalkyloxy, arylalkyloxycarbonylamino, carboxy (or an acid bioisostere), cycloalkyl, cyano, halo, heteroaryl, heteroarylalkoxy, heterocycloalkyl, hydroxy or $-NY^3Y^4$;

It will be appreciated that when m is zero the cyclic acetal system in formula (I) represents a 1,3-dioxolane ring; when m is 1 the cyclic acetal system in formula (I) represents a 1,3-dioxane; and when m is 2 the cyclic acetal system in formula (I) represents a 1,3-dioxepane.

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:-

"Patient" includes both human and other mammals.

"Acid bioisostere" means a group which has chemical and physical similarities producing broadly similar biological properties to a carboxy group (see Lipinski, Annual Reports in Medicinal Chemistry, 1986, 21, page 283 "Bioisosterism In Drug Design"; Yun, Hwahak Sekye, 1993, 33, pages 576-579 "Application Of Bioisosterism To New Drug Design"; Zhao, Huaxue Tongbao, 1995, pages 34-38 "Bioisosteric Replacement And Development Of Lead Compounds In Drug Design"; Graham, Theochem, 1995, 343, pages 105-109 "Theoretical Studies Applied To Drug Design:ab initio Electronic Distributions In Bioisosteres"). Examples of suitable acid bioisosteres include: -C(=O)-NHOH, -C(=O)-$CH_2$OH, -C(=O)-$CH_2$SH, -C(=O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, heteroarylsulphonylcarbamoyl, N-methoxycarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or heterocyclic phenols such as 3-hydroxyisoxazolyl and 3-hydoxy-1-methylpyrazolyl.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl group is as described herein.

"Acylamino" is an acyl-NH- group wherein acyl is as defined herein.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. "Branched", as used herein and throughout the text, means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear chain; here a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. Exemplary alkenyl groups include ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, heptenyl, octenyl, cyclohexylbutenyl and decenyl.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previ usly described. Exemplary alkylthio groups include methylthio, ethylthio, isopropylthio and heptylthio.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Exemplary alkynyl groups include ethynyl, propynyl, n-butynyl, i-butynyl, 3-methylbut-2-ynyl, and n-pentynyl.

"Aroyl" means an aryl-CO- group in which the aryl group is as described herein. Exemplary groups include benzoyl and 1- and 2-naphthoyl.

"Aroylamino" is an aroyl-NH- group wherein aroyl is as previously defined.

"Aryl" as a group or part of a group denotes: (i) an optionally substituted monocyclic or multicyclic aromatic carbocyclic moiety of about 6 to about 14 carbon atoms, such as phenyl or naphthyl; or (ii) an optionally substituted partially saturated multicyclic aromatic carbocyclic moiety in which an aryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure, such as a tetrahydronaphthyl, indenyl or indanyl ring. Aryl groups may be substituted with one or more aryl group substituents which may be the same or different, where "aryl group substituent" includes, for example, acyl, acylamino, alkoxy, alkoxycarbonyl, alkylenedioxy, alkylsulphinyl, alkylsulphonyl, alkylthio, aroyl, aroylamino, aryl, arylalkyloxy, arylalkyloxycarbonyl, arylalkylthio, aryloxy, aryloxycarbonyl, arylsulphinyl, arylsulphonyl, arylthio, carboxy, cyano, halo, heteroaroyl, heteroaryl, heteroarylalkyloxy, heteroaroylamino, heteroaryloxy, hydroxy, nitro, trifluoromethyl, $Y^3Y^4N$-, $Y^3Y^4NCO$-, $Y^3Y^4NSO_2$-, $Y^3Y^4N$-$C_{2-6}$alkylene-$Z^1$- (where $Z^1$ is O, $NR^5$ or $S(O)_n$), alkylC(=O)-$Y^3N$-, alkyl$SO_2$-$Y^3N$- or alkyl optionally substituted with aryl, heteroaryl, hydroxy, or $Y^3Y^4N$-. Preferred aryl group substituents within $R^1$ and $R^2$ include halogen, alkoxy, trifluoromethyl, alkylthio, alkylsulphinyl, $Y^3Y^4N$-, alkylC(=O)-$Y^3N$- or alkyl$SO_2$-$Y^3N$-, more preferably fluoro.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as previously described. Preferred arylalkyl groups contain a $C_{1-4}$alkyl moiety. Exemplary arylalkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

Preferred heteroaryl group substituents when $R^1$ or $R^2$ is pyrimidinyl include $R^{11}Z^2$- [where $R^{11}$ is alkyl, aryl, cycloalkyl, heteroaryl, heterocycl alkyl, r alkyl substituted by alkoxy, aryl, cyano, cycloalkyl, heteroaryl, heterocycloalkyl, hydroxy, oxo, $-CO_2R^7$, $-CONY^3Y^4$ or-$NY^1Y^2$ and $Z^2$ is O or $S(O)_n$] and $Y^1Y^2N$-.

"Cyclic amine" means a 3 to 8 membered monocyclic cycloalkyl ring system where one of the ring carbon atoms is replaced by nitrogen. Exemplary cyclic amines include pyrrolidine, piperidine, morpholine, piperazine, indoline and pyrindoline.

"Cycloalkenyl" means an optionally substituted non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and having about 5 to about 10 carbon atoms. Particular monocyclic cycloalkenyl rings include $C_{3-7}$cycloalkenyl such as cyclopentenyl, cyclohexenyl and cyclopentenyl. Exemplary multicyclic cycloalkenyl ring include norbornenyl. The cycloalkenyl group may be substituted by one or more substituents chosen from, for example, halo, or alkyl.

"Cycloalkyl" means an optionally substituted non-aromatic monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms. Particular monocyclic cycloalkyl rings include $C_{3-7}$cycloalkyl such as cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl. Exemplary multicyclic cycloalkyl rings include perhydronaphthyl, adamant-(1- or 2-)yl and norbornyl and spirocyclic groups (e.g. spiro[4,4]non-2yl). When $R^3$ is, or contains, a cycloalkyl ring this may particularly represent a 3 to 7 membered monocyclic ring, especially cyclohexyl. The cycloalkyl group may be substituted by one or more (e.g. 1, 2, or 3) substituents chosen from, for example, alkyl, aryl, arylalkyl, halo, halo substituted alkyl (such as trifluoromethyl), hydroxyalkyl, hydroxy, alkoxy, $-S(O)_n$-alkyl, $-NY^3Y^4$ or $-CO_2R^7$.

"Cycloalkyloxy" means a cycloalkyl-O- group in which the cycloalkyl group is as described herein. Exemplary cycloalkyloxy groups include cyclopropyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro or chloro.

"Heteroaroyl" means a heteroaryl-CO- group in which the heteroaryl group is as described herein. Exemplary groups include pyridylcarbonyl.

"Heterocycloalkyl" means a cycloalkyl group as defined above which contains one or more heteroatoms selected from O, S or $NY^5$. Particular heterocycloalkyl groups include 5-7 membered monocyclic heterocyclic groups such as cyclic ethers containing 5-7 ring members such as tetrahydrofuran and perhydropyran.

"Heterocycloalkyloxy" means a heterocycloalkyl-O- group in which the heterocycloalkyl is as previously defined.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyl groups contain $C_{1-4}$alkyl. Exemplary hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of formula (I), including N-oxides thereof. For example an ester of a compound of formula (I) containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of formula (I) containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates, methanolates, and the like.

Suitable esters of compounds of formula (I) containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates.

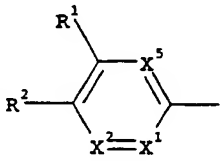
Suitable esters of compounds of formula (I) containing a carboxy group, are for example those described by F.J.Leinweber, Drug Metab. Res., 1987, 18, page 379.

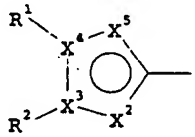
An especially useful class of esters of compounds of formula (I) containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et. al., J. Med. Chem.,

include th se derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, tetramethylammonium hydroxide, and the like.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

With reference to formula (I) above, the following are particular and preferred groupings:

Het may particularly represent  where $R^1$ and $R^2$ are as defined above, one of the atoms $X^1$, $X^2$ and $X^5$ represents N and the others independently represent N or CH. Examples of suitable ring systems include pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl.

Het may also particularly represent  where $R^1$ and $R^2$ are as defined above, $X^2$ and $X^5$ are independently CH, N, NH, O or S, and $X^3$ and $X^4$ independently represents N or C, but excluding compounds in which one of $X^2$ and $X^5$ is N and the other is NH and $X^3$ and $X^4$ are both C. Examples of suitable ring systems include furyl, imidazol-4(5)-yl, oxadiazolyl, oxazolyl, pyrazolyl, pyrrolyl, thiazolyl, thienyl and triazolyl.

One of $R^1$ and $R^2$ may particularly represent optionally substituted azaheteroaryl such as optionally substituted pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, quinazolinyl, imidazolyl or benzimidazolyl (for example optionally substituted 4-pyridyl, 4-pyrimidinyl, 4-quinolinyl, 6-isoquinolinyl, 4-quinazolinyl, 1-imidazolyl or 1-benzimidazolyl) and the other may particularly represent optionally substituted phenyl. When $R^1$ or $R^2$ represents optionally substituted

$R^3$ may also particularly represent a group $-L^1-R^6$ where $L^1$ is $C_{1-6}$alkylene, especially methylene, and $R^6$ is $-N(R^7)-C(=Z)-R^8$, in which Z, $R^7$ and $R^8$ are as defined hereinbefore, especially where Z is oxygen, $R^7$ is hydrogen and $R^8$ is alkyl, aryl or heteroaryl.

$R^3$ may also particularly represent a group $-L^1-R^6$ where $L^1$ is $C_{1-6}$alkylene, especially methylene, and $R^6$ is $-N(R^7)-C(=Z)-L^2-R^9$, in which Z, $L^2$, $R^7$, $R^8$ and $R^9$ are as defined hereinbefore, especially where Z is oxygen, $L^2$ is $C_{1-6}$alkylene, especially methylene, $R^7$ is hydrogen and $R^9$ is aryl or heteroaryl.

$R^3$ may also particularly represent a group $-L^1-R^6$ where $L^1$ is $C_{1-6}$alkylene, especially methylene, and $R^6$ is $-NHC(=Z)-NH-R^8$, in which Z and $R^8$ are as defined hereinbefore, especially where $R^8$ is alkyl, aryl or heteroaryl.

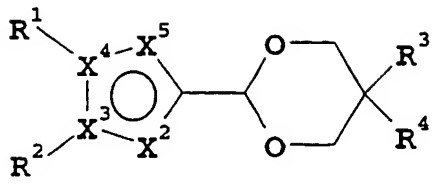
$R^3$ may also particularly represent a group $-L^1-R^6$ where $L^1$ is $C_{1-6}$alkylene, especially methylene, and $R^6$ is $-NH-C(=Z)-NH-L^2-R^9$, in which Z, $L^2$ and $R^9$ are as defined hereinbefore, especially where $L^2$ is methylene and $R^9$ is aryl or heteroaryl.

$R^3$ may also particularly represent a group $-L^1-R^6$ where $L^1$ is $C_{1-6}$alkylene, especially $C_{1-3}$alkylene, preferably methylene, and $R^6$ is $-NY^1Y^2$, where $Y^1$ and $Y^2$ are as defined hereinbefore, especially where $Y^1$ and $Y^2$ are hydrogen.

$R^3$ may also particularly represent a group $-L^1-R^6$ where $L^1$ is $C_{1-6}$alkylene, especially methylene or ethylene, and $R^6$ is aryl or heteroaryl.

$R^3$ may also particularly represent a group $-L^1-R^6$ where $L^1$ is $C_{1-6}$alkylene, especially methylene, and $R^6$ is $-N(R^7)-SO_2-R^8$, in which $R^7$ and $R^8$ are as defined hereinbefore, especially where $R^7$ is hydrogen and $R^8$ is alkyl, aryl or heteroaryl.

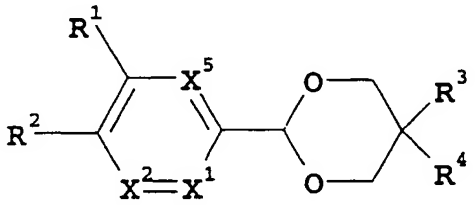
$R^3$ may also particularly represent a group $-L^1-R^6$ where $L^1$ is $C_{1-6}$alkylene, especially methylene, and $R^6$ is $-N(R^7)-SO_2-L^2-R^8$, in which $L^2$, $R^7$ and $R^8$ are as defined hereinbefore, especially where $L^2$ is methylene, $R^7$ is hydrogen and $R^8$ is alkyl, aryl or heteroaryl.



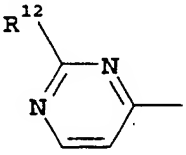
(Ib)

in which $R^3$, $R^4$, $X^2$, $X^3$, $X^4$ and $X^5$ are as hereinbefore defined, one of $R^1$ and $R^2$ is 4-pyridyl and the other is 4-fluorophenyl, and N-oxides thereof, and their prodrugs; and pharmaceutically acceptable salts and solvates (e.g. hydrates) of compounds of formula (Ib) and N-oxides thereof, and their prodrugs.

A further particular group of compounds of the invention are compounds of formula (Ic)



(Ic)

in which $R^3$, $R^4$, $X^1$, $X^2$ and $X^5$ are as hereinbefore defined, one of $R^1$ and $R^2$ is 4-fluorophenyl and the other is  in which $R^{12}$ is $R^{11}Z^2$- or $Y^1Y^2N$- ( wherein $R^{11}$, $Y^1$, $Y^2$ and $Z^2$ are as hereinbefore defined), and N-oxides thereof, and their prodrugs; and pharmaceutically acceptable salts and solvates (e.g. hydrates) of compounds of formula (Ic) and N-oxides thereof, and their prodrugs.

A particular group of compounds of the invention are those selected from the following:
4-[5-(5,5-dimethyl-[1,3]dioxan-2-yl)-2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-pyridine;
4-[5-(5,5-dimethyl-[1,3]dioxan-2-yl)-2-(4-fluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-pyridine;
4-[2-(5,5-dimethyl-[1,3]dioxan-2-yl)-5-(4-fluoro-phenyl)-oxazol-4-yl]-pyridine;
4-[2-(5,5-dimethyl-[1,3]dioxan-2-yl)-4-(4-fluoro-phenyl)-oxazol-5-yl]-pyridine;
{2-[1-(4-fluoro-phenyl)-5-pyridin-4-yl-4H-pyrazol-3-yl]-5-methyl-[1,3]dioxan-5-yl}-morpholin-4-yl-methanone;
{2-[1-(4-fluoro-phenyl)-5-pyridin-4-yl-1H-[1,2,4]triazol-3-yl]-5-methyl-[1,3]dioxan-5-yl}-morpholin-4-yl-methanone;
{2-[5-(4-fluoro-phenyl)-4-pyridin-4-yl-oxazol-2-yl]-5-methyl-[1,3]dioxan-5-yl}-morpholin-4-yl-methanone;
{2-[4-(4-fluoro-phenyl)-5-pyridin-4-yl-oxazol-2-yl]-5-methyl-[1,3]dioxan-5-yl}-morpholin-4-yl-methanone;
cyclopropyl-{4-[5-(5,5-dimethyl-[1,3]dioxan-2-yl)-2-(4-fluoro-phenyl)-4H-pyrazol-3-yl]-pyrimidin-2-yl}-amine;
cyclopropyl-{4-[5-(5,5-dimethyl-[1,3]dioxan-2-yl)-2-(4-fluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-pyrimidin-2-yl}-amine;
cyclopropyl-{4-[2-(5,5-dimethyl-[1,3]dioxan-2-yl)-5-(4-fluoro-phenyl)-oxazol-4-yl]-pyrimidin-2-yl}-amine;
cyclopropyl-{4-[2-(5,5-dimethyl-[1,3]dioxan-2-yl)-4-(4-fluoro-phenyl)- oxazol-5-yl]-pyrimidin-2-yl}-amine;
2-{1-(4-fluoro-phenyl)-5-[2-(2-methoxy-ethylamino)-pyrimidin-4-yl]-1H-pyrazol-3-yl}-5-methyl-[1,3]dioxane-5-carboxylic acid propylamide;
2-{1-(4-fluoro-phenyl)-5-[2-(2-methoxy-ethylamino)-pyrimidin-4-yl]-1H-[1,2,4]triazol-3-yl}-5-methyl-[1,3]dioxane-5-carboxylic acid propylamide;
2-{5-(4-fluoro-phenyl)-4-[2-(2-methoxy-ethylamino)-pyrimidin-4-yl]-oxazol-2-yl}-5-methyl-[1,3]dioxane-5-carboxylic acid propylamide;
2-{4-(4-fluoro-phenyl)-5-[2-(2-methoxy-ethylamino)-pyrimidin-4-yl]-oxazol-2-yl}-5-methyl-[1,3]dioxane-5-carboxylic acid propylamide;
2-[1-(4-fluoro-phenyl)-5-(2-propylamino-pyrimidin-4-yl)-1H-pyrazol-3-yl]-5-methyl-[1,3]dioxane-5-carboxylic acid cyclopropylamide;
2-[1-(4-fluoro-phenyl)-5-(2-propylamino-pyrimidin-4-yl)-1H-[1,2,4]triazol-3-yl]-5-methyl-[1,3]dioxane-5-carboxylic acid cyclopropylamide;
2-[5-(4-fluoro-phenyl)-4-(2-propylamino-pyrimidin-4-yl)-oxazol-2-yl]-5-methyl-[1,3]dioxane-5-carboxylic acid cyclopropylamide;

conditions such as rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis and steoarthritis. Additionally, the compounds are useful in the treatment of acute synovitis, tuberculosis, atherosclerosis, muscle degeneration, cachexia, Reiter's syndrome, endotoxaemia, sepsis, septic shock, endotoxic shock, gram negative sepsis, gout, toxic shock syndrome, chronic pulmonary inflammatory diseases including asthma and adult respiratory distress syndrome, silicosis, pulmonary sarcoidosis, bone resorption diseases, osteoporosis, restenosis, heart failure and myocardial ischaemic syndromes, cardiac and renal reperfusion injury, thrombosis, glomerularnephritis, graft vs. host reaction, allograft rejection and leprosy. Furthermore, the compounds are useful in the treatment of infections such as viral infections, for example HIV, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, parasitic infections, for example malaria such as cerebral malaria, and yeast and fungal infections, for example fungal meningitis; fever and myalgias due to infection; AIDS; AIDS related complex (ARC); cachexia secondary to infection or malignancy; cachexia secondary to acquired immune deficiency syndrome (AIDS) or to cancer; keloid and scar tissue formation; pyresis; diabetes; inflammatory bowel diseases such as Crohn's disease and ulcerative colitis; eczema; contact dermititis; psoriasis; sunburn and conjunctivitis.

Compounds of the invention are also useful in the treatment of diseases of, or injury to, the brain in which over-production of TNF-alpha has been implicated, such as multiple sclerosis, Alzheimers disease, trauma, stroke and other ischaemic conditions.

Compounds of the invention may also be useful in inhibiting diseases associated with over-production of other pro-inflammatory cytokines, IL-1, IL-6 and IL-8.

A special embodiment of the therapeutic methods of the present invention is the treating of asthma.

Another special embodiment of the therapeutic methods of the present invention is the treating of joint inflammation.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of TNF, especially TNF-alpha, for example conditions as hereinbefore described, which comprises the administration to the patient of an effective amount of compound of the invention or a composition containing a compound of the invention.

used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

For topical administration, gels (water or alcohol based), creams or ointments containing compounds of the invention may be used. Compounds of the invention may also be incorporated in a gel or matrix base for application in a patch, which would allow a controlled release of compound through the transdermal barrier.

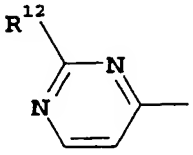
For administration by inhalation compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of the invention.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.001 to about 50, preferably about 0.001 to about 5, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.001 to about 10, preferably 0.01 to 1, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

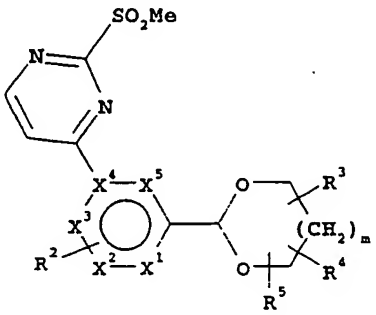
The compounds according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with

As another example, compounds of formula (I), in which within Het $R^1$ represents



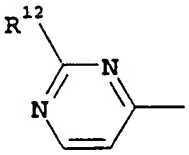
wherein $R^{12}$ is $Y^4Y^5N$- [in which $Y^4$ and $Y^5$ are as defined in formula (I)],

may be prepared by reaction of a compound of formula (IV):-



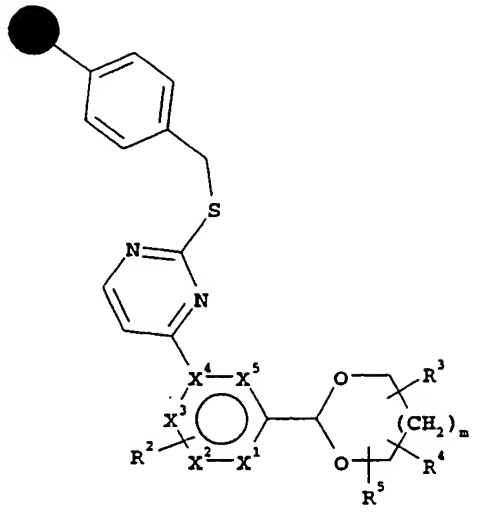
(IV)

wherein $R^2$, $R^4$, $R^5$, $X^1$, $X^2$, $X^3$, $X^4$ and $X^5$ are as defined in formula (I), with an amine of formula $HNY^4Y^5$ wherein $Y^4$ and $Y^5$ are as just hereinbefore defined. The reaction may conveniently be carried out in an inert solvent such as dimethylformamide at a temperature up to about 100°C. When $Y^5$ is hydrogen the reaction may be conveniently carried out in a sealed vessel. When $Y^5$ is aryl, for example phenyl, the reaction may be conveniently carried out with the lithio-anion of the amine.

Alternatively, compounds of formula (I), in which within Het $R^1$ represents 

wherein $R^{12}$ is $Y^4Y^5N$- [in which $Y^4$ and $Y^5$ are as defined in formula (I)], may be prepared by

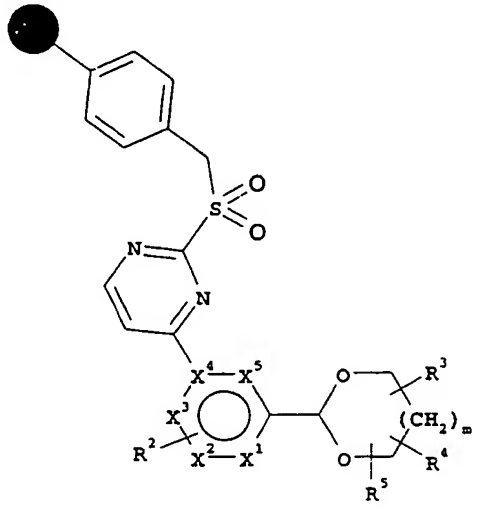
(i) treating Merrifield resin (chloromethylated styrene/divinylbenzene copolymer) with potassium thioacetate in an inert solvent, such as dimethylformamide, at a temperature at about room temperature, to give Resin A;



Resin C

in which $R^2$, $R^3$, $R^4$, $R^5$ and m are as defined in (IV) above; followed by appropriate functional group interconversions, for example those described hereinafter:

(iv) reacting Resin C, in which $R^2$, $R^3$, $R^4$, $R^5$ and m are as just hereinbefore defined, with m-chloroperoxybenzoic acid, in an inert solvent or preferably in a mixture of inert solvents, such as a mixture of dichloromethane and methanol, to give resin D, in which $R^2$, $R^3$, $R^4$, $R^5$ and m are as just hereinbefore defined;



Resin D

As another example of the interconversion process, compounds of formula (I) in which $R^3$ contains a $-N(R^7)-C(=O)-R^8$ or $-N(R^7)-C(=O)-L^2-R^9$ group (in which $R^7$, $R^8$, $R^9$ and $L^2$ are as defined in formula (I)), may be prepared by reacting a compound of formula (I) in which $R^3$ contains a $-NHR^7$ group (in which $R^7$ is as defined in formula (I)) with an appropriately substituted acid chloride $Cl-C(=O)-R^8$ or $Cl-C(=O)-L^2-R^9$ (in which $R^8$, $R^9$ and $L^2$ are as defined in formula (I)) in the presence of triethylamine in an inert solvent such as tetrahydrofuran and at a temperature at about room temperature.

As another example of the interconversion process, compounds of formula (I) in which $R^3$ contains a $-NH-C(=O)-R^8$ or $-NH-C(=O)-L^2-R^9$ group (in which $R^8$, $R^9$ and $L^2$ are as defined in formula (I)) may be prepared by reacting a compound of formula (I) in which $R^3$ contains a $-NH_2$ group, with an appropriately substituted acid $HO-C(=O)-R^8$ or $HO-C(=O)-L^2-R^9$ (in which $R^8$, $R^9$ and $L^2$ are as just hereinbefore defined) respectively, in the presence of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and diisopropylethylamine in dimethylformamide, at room temperature. Other standard peptide coupling procedures may be employed for the reaction, such as treatment with a carbodiimide, for example dicyclohexylcarbodiimide, in the presence of triethylamine, or treatment with 1-hydroxybenzotriazole and a carbodiimide, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, in an inert solvent such as dimethylformamide and at a temperature at about room temperature.

As another example of the interconversion process, compounds of formula (I) in which $R^3$ contains a $-NH-C(=O)-R^8$ or a $-NH-C(=O)-L^2-R^9$ group (in which $R^8$, $R^9$ and $L^2$ are as just hereinbefore defined), may be prepared by reacting a compound of formula (I) in which $R^3$ contains a $-NH_2$ group, with the appropriately substituted acid anhydride $R^8-C(=O)-O-C(=O)-R^8$ or $R^9-L^2-C(=O)-O-C(=O)-L^2-R^9$ (in which $R^8$, $R^9$ and $L^2$ are as just hereinbefore defined) in the presence of triethylamine or pyridine, in an inert solvent, such as tetrahydrofuran, and at a temperature at about room temperature.

As another example of the interconversion process, compounds of formula (I) in which $R^3$ contains a $-NH-C(=O)-NH-R^8$ or $-NH-C(=O)-NH-L^2-R^9$ group (in which $R^8$, $R^9$ and $L^2$ are as just hereinbefore defined), may be prepared by reacting a compound of formula (I) in which $R^3$

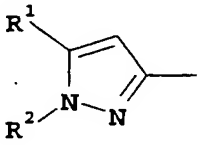
As another example of the interconversion process, compounds of formula (I) containing sulphoxide linkages may be prepared by the oxidation of a corresponding compound containing an -S- linkage. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g. 3-chloroperbenzoic acid, preferably in an inert solvent, e.g. dichloromethane, preferably at or near room temperature, or alternatively by means of potassium hydrogen peroxomonosulphate in a medium such as aqueous methanol, buffered to about pH5, at temperatures between about 0°C and room temperature. This latter method is preferred for compounds containing an acid-labile group.

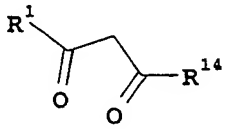
As another example of the interconversion process, compounds of formula (I) containing sulphone linkages may be prepared by the oxidation of a corresponding compounds containing an -S- or sulphoxide linkage. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g. 3-chloroperbenzoic acid, preferably in an inert solvent, e.g. dichloromethane, preferably at or near room temperature.

As another example of the interconversion process, compounds of formula (I) in which $R^3$ contains a $-N(R^7)-SO_2-R^8$ or $-N(R^7)-SO_2-L^2-R^9$ group (in which $R^7$, $R^8$, $R^9$ and $L^2$ are as defined in formula (I)), may be prepared from a corresponding compound of formula (I) in which $R^3$ contains a $-NH_2$ group by treatment with the appropriately substituted acid chloride $Cl-SO_2-R^8$ or $Cl-SO_2-L^2-R^9$ (in which $R^8$, $R^9$ and $L^2$ are as just hereinbefore defined), in the presence of a suitable base, such as triethylamine, in an inert solvent, such as tetrahydrofuran, and at a temperature at about room temperature.

It will be appreciated that compounds of the present invention may contain asymmetric centres. These asymmetric centres may independently be in either the R or S configuration. It will be apparent to those skilled in the art that certain compounds of the invention may also exhibit geometrical isomerism. It is to be understood that the present invention includes individual geometrical isomers and stereoisomers and mixtures thereof, including racemic mixtures, of compounds of formula (I) hereinabove. Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallisation techniques, or they are separately prepared from the appropriate isomers of their intermediates. Additionally, in situations where tautomers of the compounds of formula (I) are possible, the present invention is intended to include all tautomeric forms of the compounds.

Intermediates of formula (II) wherein Het is as defined in formula (I) above and $R^{13}$ is $-CH(OC_{1-4}alkyl)_2$ may be prepared by reacting a compound of formula (II) wherein Het is as just hereinbefore defined and $R^{13}$ is -CHO with a trialkylorthoformate, such as trimethyl- or triethylorthoformate in the presence of an acid catalyst, such as 4-toluene sulphonic acid, in methanol at reflux temperature.

Intermediates of formula (II) wherein Het is  [in which $R^1$ and $R^2$ are as defined in formula (I)] and $R^{13}$ is $-CH(OMe)_2$ may be prepared by reacting a compound of formula (1):-



(1)

wherein $R^1$ is as just hereinbefore defined and $R^{14}$ is $-CH(OMe)_2$, with a hydrazine of formula (2):-

$$R^2\text{-}NH\text{-}NH_2 \qquad (2)$$

wherein $R^2$ is as just hereinbefore defined, in ethanol at reflux temperature.

Compounds of formula (1) wherein $R^1$ is as just hereinbefore defined and $R^{14}$ is $-CH(OMe)_2$ may be prepared by reacting a compound of formula (3):-

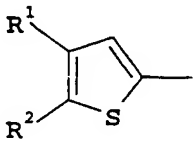
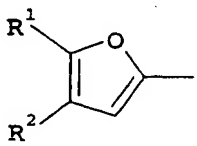
$$R^1\text{-}C(=O)\text{-}CH_3 \qquad (3)$$

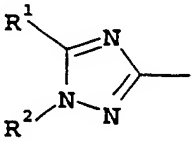
wherein $R^1$ is as just hereinbefore defined, with methyl dimethoxyacetate in the presence of a suitable base, such as lithium bis (trimethylsilyl)amide, in an inert solvent, such as tetrahydrofuran, and at a temperature from about -40°C to about room temperature. This reaction is particularly suitable for the preparation of compounds of formula (1) where $R^1$ is pyridyl.

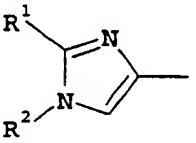
Intermediates of formula (II) wherein Het is as defined in formula (I) and $R^{13}$ is -CHO may also be prepared by reduction of a corresponding ester of formula (6):-

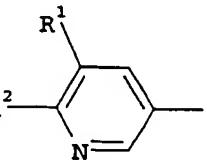
$$Het\text{-}CO_2R^{15} \qquad (6)$$

wherein Het is as defined immediately hereinabove and $R^{15}$ is alkyl, preferably methyl or ethyl, using standard methodologies (e.g. those described in Comprehensive Organic Transformations, R.C. Larock, page 621).

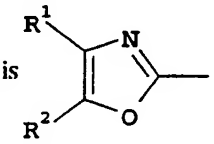
Esters of formula (6) wherein Het is  or  [in which $R^1$ and $R^2$ are as defined in formula (I)] and $R^{15}$ is alkyl may be prepared by the application or adaptation of the methods described in the specification of European Patent Application No. EP 728755.

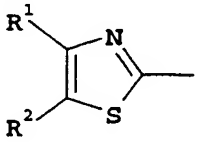
Esters of formula (6) wherein Het is  [in which $R^1$ and $R^2$ are as defined in formula (I)] and $R^{15}$ is alkyl may be prepared by the application or adaptation of methods described by Bruche, Luca et al., Synthesis, 1985, 3, 304-5.

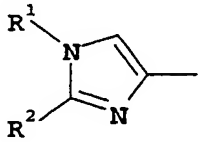
Esters of formula (6) wherein Het is  [in which $R^1$ and $R^2$ are as defined in formula (I)] and $R^{15}$ is alkyl may be prepared by the application or adaptation of methods described by I.K.Khanna et al., J.Med.Chem., 1997, 40, pages 1634-1647.

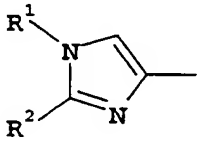
Esters of formula (6) wherein Het is  [in which $R^1$ and $R^2$ are as defined in formula (I)] and $R^{15}$ is alkyl may be prepared by the application or adaptation of methods described in the specification of International Patent Application Publication No. WO 98/03484.

wherein Het is as defined immediately hereinab ve using standard methodologies, for example those described in Comprehensive Organic Transformations , R.C. Larock, page 604.

Compounds of formula (8) wherein Het is  [in which $R^1$ and $R^2$ are as defined in formula (I)] may be prepared by adaptation of the methods described by Norman, B.H. in US Patent No. 5719163.

Intermediates of formula (II) wherein Het is  [in which $R^1$ and $R^2$ are as defined in formula (I)] and $R^{13}$ is -CHO may be prepared by adaptation of the methods described by V.Cecchetti et al., Bioorg. Med. Chem., 1994, 2, pages 799-806.

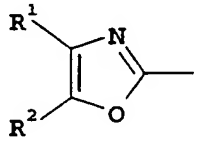
4-Formylimidazoles of formula (II) wherein Het is  [in which $R^1$ and $R^2$ are as defined in formula (I)] and $R^{13}$ is -CHO may be prepared by adaptation of the methods described by C.Gonczi. J. Org. Chem., 1981, 46, pages 608-610.

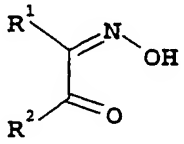
4-Formylimidazoles of formula (II) wherein Het is  [in which $R^1$ and $R^2$ are as defined in formula (I)] and $R^{13}$ is -CHO may also be prepared by the application or adaptation of methods described by I.K.Khanna et al., J.Med.Chem., 1997, 40, pages 1634-1647.

Intermediates of formula (II) wherein Het is as defined in formula (I) and $R^{13}$ is -CHO may be prepared by Vilsmeyer formylation of the corresponding compounds formula (9):-

Het-H (9)

Compounds f formula (11) wherein $R^1$ and $R^2$ are as defined in formula (I) may be prepared by the application or adaptation of the methods described in the specification of International Patent Application No. WO98/56788 for Reference Examples 9 and 11.

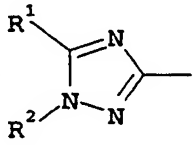
Oxazole derivatives of formula (9) wherein Het is  [in which $R^1$ and $R^2$ are as defined in formula (I)] may be prepared by reaction of compounds of formula (12):-

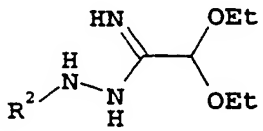


(12)

wherein $R^1$ and $R^2$ are as just hereinbefore defined, with zinc in formic acid at a temperature at about reflux temperature.

Compounds of formula (12) wherein $R^1$ and $R^2$ are as defined in formula (I) may be prepared by reaction of compounds of formula (11) wherein $R^1$ and $R^2$ are as defined in formula (I) with sodium nitrite in water at a temperature at about 10°C.

Intermediates of formula (II) wherein Het is  [in which $R^1$ and $R^2$ are as defined in formula (I)] and $R^{13}$ is $-CH(OEt)_2$ may be prepared by reacting compounds of formula (13):-



(13)

wherein $R^2$ is as just hereinbefore defined with acid halides of formula (14):-

such as dicyclohexylcarbodiimide, in the presence of 1-hydroxybenzotriazole and disisopropylethylamine, in an inert solvent, such as acetonitrile, and at a temperature from room temperature to about 55°C. Other standard peptide coupling procedures may be employed for the reaction, such as those described hereinbefore.

Resins of formula Resin C in which $R^2$, $R^4$, $R^5$ and m are as hereinbefore defined, and $R^3$ contains a -C(=O)-$NY^4Y^5$ group may be prepared from a corresponding Resin C, in which $R^2$, $R^4$, $R^5$ and m are as hereinbefore defined and $R^3$ contains a -C(=O)-$OR^{14}$ group (in which $R^{14}$ is alkyl, aryl or arylalkyl), by:- (i) treatment with an alkali metal hydroxide, such as sodium hydroxide, in a mixture of water and a water miscible inert organic solvent, such as tetrahydrofuran, and at a temperature from about room temperature to about 70°C; (ii) treatment of the resulting resin in which $R^3$ contains a -C(=O)-OH group with oxalyl chloride solution in an inert solvent, such as dichloromethane, at a temperature at about room temperature; (iii) treatment of the resulting resin in which $R^3$ contains a -C(=O)-Cl group with an amine of formula $HNY^4Y^5$ in an inert solvent, such as dichloromethane, at a temperature at about room temperature.

Resins of formula Resin C in which $R^2$, $R^4$, $R^5$ and m are as hereinbefore defined, and $R^3$ contains a -N($R^7$)-C(=O)-$R^8$ or -N($R^7$)-C(=O)-$L^2$-$R^9$ group (in which $R^7$, $R^8$, $R^9$ and $L^2$ are as hereinbefore defined), may be prepared from a corresponding Resin C, in which $R^2$, $R^4$, $R^5$ and m are as hereinbefore defined and $R^3$ contains a -$NH_2$ group by treatment with the appropriately substituted acid chloride Cl-C(=O)-$R^8$ or Cl-C(=O)-$L^2$-$R^9$ (in which $R^8$, $R^9$ and $L^2$ are as hereinbefore defined), in the presence of triethylamine, in an inert solvent, such as tetrahydrofuran, and at a temperature at about room temperature.

Resins of formula Resin C in which $R^2$, $R^4$, $R^5$ and m are as hereinbefore defined, and $R^3$ contains a -N($R^7$)-$SO_2$-$R^8$ or -N($R^7$)-$SO_2$-$L^2$-$R^9$ group (in which $R^7$, $R^8$, $R^9$ and $L^2$ are as hereinbefore defined), may be prepared from a corresponding Resin C, in which $R^2$, $R^4$, $R^5$ and m are as hereinbefore defined and $R^3$ contains a -$NH_2$ group by treatment with the appropriately substituted sulphonyl chloride Cl-$SO_2$-$R^8$ or Cl-$SO_2$-$L^2$-$R^9$ (in which $R^8$, $R^9$ and $L^2$ are as hereinbefore defined), in the presence of triethylamine, in an inert solvent, such as tetrahydrofuran, and at a temperature at about room temperature.

(50ml) and saturated aqueous sodium carbonate solution (50ml). The rganic phase was washed three times with water (50ml), then dried ver magnesium sulphate and then evaporated. The residual oil was triturated twice with diethyl ether then recrystallised from diethyl ether to give the title compound as white needles (1g), m.p. 150-151°C. [Elemental analysis:- C,67.69; H,5.98; N,12.09%. Calculated for $C_{20}H_{20}FN_3O_2$:- C,67.97; H,5.70; N,11.89%]. MS: 354 $[MH]^+$. $R_F$ = 0.42 (ethyl acetate, determined by thin layer chromatography on silica).

(b) by proceeding in a similar manner to Example 1(a) but using 4-[5-diethoxymethyl-2-(4-fluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-pyridine (Reference Example 3) there was prepared 4-[5-(5,5-dimethyl-[1,3]dioxan-2-yl)-2-(4-fluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-pyridine as a yellow solid, m.p. 125-127°C. [Elemental analysis:- C, 64.38; H, 5.48; N, 16.11%. Calculated for $C_{19}H_{19}FN_4O_2$:- C, 64.40; H, 5.40; N, 15.81%]. MS: 355 $[MH]^+$. $R_F$ = 0.42 (ethyl acetate, determined by thin layer chromatography on silica).

(c) by proceeding in a similar manner to Example 1(a) but using 4-[2-formyl-5-(4-fluoro-phenyl)-oxazol-4-yl]-pyridine [Reference Example 5(a)] there was prepared 4-[2-(5,5-dimethyl-[1,3]dioxan-2-yl)-5-(4-fluoro-phenyl)-oxazol-4-yl]-pyridine as a yellow solid, m.p. 141.2-142.5°C. [Elemental analysis:- C, 67.44; H, 5.18; N, 7.87%. Calculated for $C_{20}H_{19}FN_2O_3$:- C, 67.79; H, 5.40; N, 7.90%]. MS: 355 $[MH]^+$. $R_F$ = 0.28 (ethyl acetate, determined by thin layer chromatography on silica).

(d) by proceeding in a similar manner to Example 1(a) but using 4-[2-formyl-4-(4-fluoro-phenyl)-oxazol-5-yl]-pyridine [0.9g, Reference Example 5(b)] and subjecting the crude reaction product to flash chromatography on silica eluting with ethylacetate followed by recrystallisataion from diethyl ether there was prepared 4-[2-(5,5-dimethyl-[1,3]dioxan-2-yl)-4-(4-fluoro-phenyl)-oxazol-5-yl]-pyridine as a white solid, m.p. 138-140°C. MS: 355 $[MH]^+$. $R_F$ = 0.42 (ethyl acetate, determined by thin layer chromatography on silica).

(e) by proceeding in a similar manner to Example 1(a) but reacting (i) 4-[5-dimethoxymethyl-2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-pyridine, (ii) 4-[5-diethoxymethyl-2-(4-fluoro-phenyl)-2H-[1,2,4]triazol-3-yl]-pyridine, (iii) 4-[2-formyl-5-(4-fluoro-phenyl)-oxazol-4-yl]-pyridine or (iv) 4-[2-formyl-4-(4-fluoro-phenyl)-oxazol-5-yl]-pyridine with 3-hydroxy-2-(hydroxymethyl)-2-methyl-1-morpholino-1-propanone (prepared according to the method described for Reference Example 6 in International Patent Application No. WO98/56788) instead of 2,2-dimethylpropane-1,3-diol there may be prepared [2-[1-(4-fluoro-phenyl)-5-pyridin-4-yl-

## REFERENCE EXAMPLE 4

4-Fluorophenylhydrazino-diethoxyacetamidine

A solution of methyl diethoxyacetimidate (4.5g, prepared according to the procedure described by Schaefer et al., J.Org.Chem., 1961, 26, pages 412-418) in methanol (150ml) was treated with 4-fluorophenylhydrazine hydrochloride (4.53g). After standing at room temperature for 16 hours the mixture was evaporated. The residue was treated with ethyl acetate and filtered. The filtrate was evaporated to give the title compound as a yellow oil. MS: 256 $[MH^+]$.

## REFERENCE EXAMPLE 5

(a) 4-[2-Formyl-5-(4-fluoro-phenyl)-oxazol-4-yl]-pyridine (compound H)

A stirred solution of 4-[5-(4-fluoro-phenyl)-oxazol-4-yl]-pyridine (1.5g, Reference Example 6) in dry tetrahydrofuran (50ml), under an inert atmosphere and at -10°C, was treated with a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (12.5ml, 1M). After 0.5 hour the mixture was treated with N-formylmorpholine (1.5ml). This mixture was stirred at room temperature for 16 hours then treated with diethyl ether (50ml) and then filtered. The solid was suspended in 10% aqueous ammonium chloride solution (50ml) and the resulting yellow solid filtered to give the title compound. MS: 269 $[MH^+]$.

(b) by proceeding in a similar manner to Reference Example 5(a) but using 4-[4-(4-fluoro-phenyl)-oxazol-5-yl]-pyridine (Reference Example 8) there was prepared 4-[2-formyl-4-(4-fluoro-phenyl)-oxazol-5-yl]-pyridine. MS: 269 $[MH^+]$.

## REFERENCE EXAMPLE 6

4-[5-(4-Fluoro-phenyl)-oxazol-4-yl]-pyridine

To a solution of 1-(4-fluoro-phenyl)-2-pyridin-4-yl-ethane-1,2-dione 1-oxime (4.88g, Reference Example 7) in formic acid (150ml) was added zinc (3.9g) and the resulting mixture was refluxed for 6 hours. The solvent was then evaporated, the residue taken up into ethyl acetate and the grey solid discarded. The solvent was evaporated and the oil was subjected to flash chromatography on silica eluting with ethyl acetate to give the title compound as a white solid. MS: 241 $[MH]^+$. $R_F$ = 0.28 (ethyl acetate, determined by thin layer chromatography on silica).

## REFERENCE EXAMPLE 7

1-(4-Fluoro-phenyl)-2-pyridin-4-yl-ethane-1,2-dione 1-oxime

A solution of 1-(4-fluoro-phenyl)-2-pyridin-4-yl-ethanone (6.45g, prepared according to the method described for Reference Example 11 in the specification of International Patent

(HBSS) supplemented with deoxyribonuclease (37.5 U/ml) and human serum albumin (0.3%). Differential (cytospin) cell c unts revealed that the mononuclear cell fraction routinely comprised 70-80% monocytes.

Cells from the mononuclear leukocyte fraction were centrifuged (200g, 10min, 20°C), resuspended, at a density of $10^6$ cells/ml. in RPMI 1640 containing foetal calf serum (FCS) (1% ), penicillin (50 U/ml) and streptomycin (50 µg/ml) and allowed to adhere in 96 well plates. Following incubation (5% $CO_2$, 37°C) for 90minutes, medium containing non-adherent cells was removed, the cells were washed once with fresh medium and fresh medium was added.

1.2. Measurement of monocyte TNF-alpha release

Adherent cells in culture medium were incubated for 1 hour (5% $CO_2$, 37°C) with fresh medium containing compounds or vehicle (0.1 % dimethylsulphoxide). Compounds were tested within the concentration range of $3x10^{-9}$M to $3x10^{-6}$M. LPS (10 ng/ml) was then added to the cells and the incubation continued for a further 18 hours. Cell supernatants were removed into 96 well, 0.22 µm filtration plates for storage at -20°C.

TNF-alpha concentrations in cell supernatants were quantified by sandwich ELISA. Briefly, ELISA plates were coated overnight with 2µg/ml of mouse anti-human TNF-alpha antibody in bicarbonate buffer (pH 9.9). After washing the wells with wash buffer (0.05% (v/v) Tween in PBS),and blocking unoccupied sites (1% BSA in PBS), monocyte supernatant samples or human recombinant TNF-alpha standards were vacuum filtered into the corresponding wells of the ELISA plate. Biotinylated rabbit polyclonal anti-human TNF-alpha antibody (3 µg/ml) was used as the second antibody and streptavidin-horseradish peroxidase was used as the detection antibody. The peroxidase substrate was 3.3',5,5'-tetramethylbenzidine (TMB), in the presence of hydrogen peroxide.

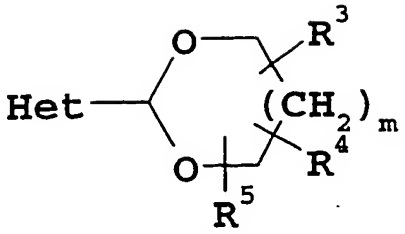
TNFα concentrations in supernatants from control and LPS-stimulated monocyte incubations were calculated by interpolation from a standard (log/log) curve (0.125-16 ng/ml) fitted by linear regression using a Multicalc software program (Wallac U.K., Ltd).

1.3. Results

Compounds within the scope of the invention produce 50% inhibition of LPS induced TNF-alpha release from human monocytes at concentrations within the range of $10^{-9}$ M to $10^{-4}$ M, preferably within the range of $10^{-9}$ M to $10^{-7}$ M.

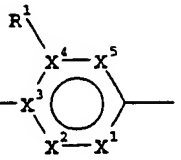
CLAIMS

1. A compound of formula (I):



(I)

wherein:-

Het is a five or six membered heteroaromatic ring of the formula  in which

one of $R^1$ and $R^2$ is optionally substituted heteroaryl and the other is optionally substituted heteroaryl or optionally substituted aryl; $X^1$ is a bond, $X^3$ and $X^4$ are each independently N or C and $X^2$ and $X^5$ are independently CH, N, NH, O or S; or $X^3$ and $X^4$ are C, one of $X^1$, $X^2$ and $X^5$ is N and the others are N or CH; but excluding compounds in which $X^1$ is a bond, one of $X^2$ and $X^5$ is N and the other is NH and $X^3$ and $X^4$ are both C;

$R^3$ represents a group $-L^1-R^6$;

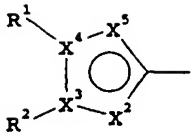
$R^4$ represents hydrogen, alkyl or hydroxyalkyl; or

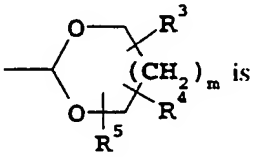
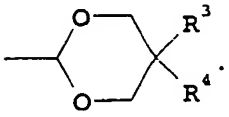
$R^3$ and $R^4$, when attached to the same carbon atom, may form with the said carbon atom a cycloalkyl, cycloalkenyl or heterocycloalkyl ring or a group $C=CH_2$;

$R^5$ represents hydrogen or alkyl;

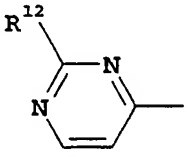
$R^6$ is hydrogen, alkyl, azido, hydroxy, alkoxy, aryl, arylalkyloxy, aryloxy, carboxy (or an acid bioisostere), cycloalkyl, cycloalkyloxy, heteroaryl, heteroarylalkyloxy, heteroaryloxy, heterocycloalkyl, heterocycloalkyloxy, nitro, $-NY^1Y^2$, $-N(R^7)-C(=Z)-R^8$, $-N(R^7)-C(=Z)-L^2-R^9$, $-NH-C(=Z)-NH-R^8$, $-NH-C(=Z)-NH-L^2-R^9$, $-N(R^7)-SO_2-R^8$, $-N(R^7)-SO_2-L^2-R^9$, $-S(O)_nR^{10}$, $-C(=Z)-NY^1Y^2$ or $-C(=Z)-OR^{10}$;

$R^7$ is hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl, heteroarylalkyl, or heterocycloalkyl;

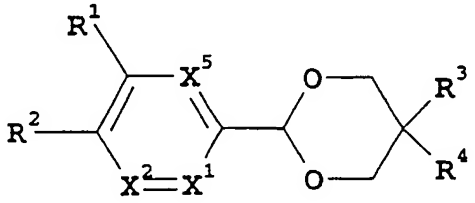
3. A compound according to Claim 1 in which Het represents  wherein $X^2$ and $X^5$ are independently CH, N, NH, O or S, and $X^3$ and $X^4$ independently represents N or C, but excluding compounds in which one of $X^2$ and $X^5$ is N and the other is NH and $X^3$ and $X^4$ are both C.

4. A compound according to any preceding claim in which the ring  is  .

5. A compound according to any preceding claim in which one of $R^1$ and $R^2$ is 4-pyridyl and the other is 4-fluorophenyl.

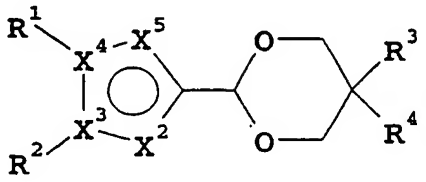
6. A compound according to any one of Claims 1 to 4 in which one of $R^1$ and $R^2$ is 4-fluorophenyl and the other is  [wherein $R^{12}$ is $R^{11}Z^2$- (in which $R^{11}$ is alkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, or alkyl substituted by alkoxy, aryl, cyano, cycloalkyl, heteroaryl, heterocycloalkyl, hydroxy, oxo, $-CO_2R^7$, $-CONY^3Y^4$ or $-NY^1Y^2$ and $Z^2$ is O or $S(O)_n$) or $Y^1Y^2N$- and $Y^1$ to $Y^4$, $R^7$ and n are as defined in Claim 1].

7. A compound according to Claim 1 having the formula (Ia)

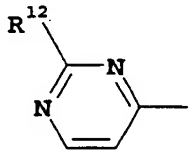


(Ia)

10. A compound according to Claim 1 having the formula (Id)



(Id)

in which $R^3$, $R^4$, $X^2$, $X^3$, $X^4$ and $X^5$ are as defined in Claim 1, one of $R^1$ and $R^2$ is 4-fluorophenyl and the other is  [wherein $R^{12}$ is $Y^1Y^2N$- in which $Y^1$ and $Y^2$ are as defined in Claim 1], and N-oxides thereof, and their prodrugs; and pharmaceutically acceptable salts and solvates of compounds of formula (Id) and N-oxides thereof, and their prodrugs.

11. A compound according to any preceding claim in which $R^3$ and $R^4$ are both $C_{1-4}$alkyl groups.

12. A compound according to any one of Claims 1 to 10 in which $R^3$ is -C(=O)-$NY^1Y^2$ (where $Y^1$ and $Y^2$ are as defined in Claim 1) and $R^4$ is $C_{1-4}$alkyl.

13. A compound according to Claim 12 in which $Y^1$ is hydrogen and $Y^2$ is alkyl or cycloalkyl.

14. A compound according to Claim 12 in which the group -$NY^1Y^2$ forms a 5-7 membered cyclic amine containing a further heteroatom selected from O or $NY^5$ (where $Y^5$ is H or alkyl).

15. A pharmaceutical composition comprising a compound according to Claim 1 together with a pharmaceutically acceptable carrier or excipient.

16. A pharmaceutical composition for use in the treatment of a condition which can be ameliorated by the administration of an inhibitor of TNF-alpha comprising an effective amount of the compound according to Claim 1.